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| 10/706,328 | 11/12/2003 | Alison Hannah | 072121-0366 | 6441 |

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| EXAMINER | |
|---|---|
| LEWIS, AMY A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1614 | |

DATE MAILED: 12/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/706,328 | HANNAH ET AL. | |
| | Examiner | Art Unit | |
| | Amy A. Lewis | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *39-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38 and 49-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-58* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *A-E and 12/22/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-38 and 49-58, drawn to a method of treating cancer by administering the receptor tyrosine kinase inhibitor 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazole-2-yl]quinolin-2(1H)-one, classified in class 514, subclass 311.

II. Claims 39-43, drawn to a method of determining a metabolic profile for the compound 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazole-2-yl]quinolin-2(1H)-one, classified in class 435, subclass 7.21 or 7.23.

III. Claims 44-48, drawn to a method of determining the amount of the compound 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazole-2-yl]quinolin-2(1H)-one in a tissue sample, classified in class 435, subclass 4.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are patentably distinct and/or independent. Invention I is drawn to a method of treating cancer by administering 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazole-2-yl]quinolin-2(1H)-one and Invention II is drawn to an a method of determining the metabolic profile for the compound. These methods are distinct since the practice of Invention I does not require the particulars of the method for determining the metabolic profile of the recited compound of Invention II, nor does the method of determining the metabolic

profile of Invention II require the practice *per se* of the method of treatment of Invention I. For example, one would not need to determine the metabolic profile of the recited compound (of Invention II) in order to administer the compound in a cancer treatment therapy. Nor would one necessarily need to administer the compound in a cancer treatment therapy after determining the metabolic profile in a subject; one could just determine the metabolic profile of the compound in the subject.

Inventions I and III are patentably distinct and/or independent. Invention I is drawn to a method of treating cancer by administering 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazole-2-yl]quinolin-2(1H)-one and Invention III Invention III is drawn to a method of determining the amount of the compound in a tissue sample. These methods are distinct since the practice of Invention I does not require the particulars of the method of measuring the amount of compound of Invention III, nor does the method of measuring of Invention III require the practice *per se* of the method treatment of Invention I. For example, one would not need to determine measure the amount of the compound in a tissue sample (of Invention III) in order to administer the compound in a cancer treatment therapy. Nor would one necessarily need to administer the compound in a cancer treatment therapy after measuring the amount of the compound in a tissue sample; one could just determine the measure the amount of the compound present in the sample.

Inventions II and III are patentably distinct and/or independent. Invention II is drawn to an a method of determining the metabolic profile for the compound 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazole-2-yl]quinolin-2(1H)-one, and Invention III is drawn to a method of determining the amount of the compound 4-amino-5-fluoro-3-[6-(4-

methylpiperazin-1-yl)-1H-benzimidazole-2-yl]quinolin-2(1H)-one in a tissue sample. These methods are distinct since the practice of Invention III does not require the particulars of the method determining the metabolic profile of Invention II, nor does the method of measuring of Invention III require the practice *per se* of the method of determining the metabolic profile of Invention II. For example, one could simply measure the amount of the compound and not do any further testing to determine the metabolic profile.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Young Suh on 7 November 2005 a provisional election was made without traverse to prosecute the invention of Group I (claims 1-38 and 49-58). Affirmation of this election must be made by applicant in replying to this Office action. Claims 39-48 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 9, 30, 49, 52, 53, and 56-58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 4, and 7-9 of copending Application No. 10/839793. Although the conflicting claims are not identical, they are not patentably distinct from each other because they both teach a method of treating cancer with the same composition, namely 4-amino-5-fluoro-3-[5-(4-methyl-4-oxidopiperizin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, and tautomers thereof.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant needs to file a terminal disclaimer over each of the patents to obviate the rejections. In addition, Applicant is advised to review all pending application for issues of double type patenting. The following is a list of known applications/patents with obviousness type double patenting issues:

US Patent Nos.:

6605617
6774237
6762194
6800760

US Patent Application Nos.:

10/644055
10/982543

An appropriate terminal disclaimer over each of the above is needed because the claims of this application conflict with claims of the above indicated applications. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application, maintain a clear line of demarcation between the applications, or file the terminal disclaimers. See MPEP § 822.

***Claim Rejections - 35 USC § 112, 1st paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1) Claims 1-38 and 49-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating breast, ovarian, chronic myeloid leukemia (CML), acute myeloid leukemia (AML), multiple myeloma, colon, prostate, lung, and brain cancers in various cell lines and in an *in vivo* mouse xenograft model with the claimed quinolinone compound, does not reasonably provide enablement for treating or inhibiting the growth of all types of cancer, cancer cells, or tumors with the claimed quinolinone compound.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) Nature of the invention.
2) State of the prior art.
3) Relative skill of those in the art.
4) Level of predictability in the art.
5) Amount of direction or guidance provided by the inventor.
6) Presence or absence of working examples.
7) Breadth of the claims.
8) Quantity of experimentation necessary to make or use the invention based on the content of the disclosure.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow.

*1) The nature of the invention.*

The claimed invention relates generally to chemotherapy, and specifically to compositions and methods for inhibiting the proliferation of cancer cells and tumor growth without regard to the environment (see instant claim 1) which includes both *in vitro* and *in vivo*.

*2) State of the prior art.*

While the state of the art is relatively high with regard to the treatment of specific

cancer types, the state of the art with regard to treating cancer broadly is underdeveloped. In particular, there is no known anticancer agent that is effective against all cancer cell types. The Cecil reference (Cecil Textbook of Medicine, 21st Edition (2000), Goldman & Bennett (Editors), W.B. Saunders Company (Publisher), Chapter 198, pages 1060-1074) clearly shows that for the various known cancer types, there is no one specific chemotherapeutic agent that is effective for all types of cancer (see page Table 198-5 at page 1065; Tables 198-6 and 198-7 at page 1066; Table 198-8 at page 1068; and Table 198-9 at page 1071).

*3) Relative skill of those in the art.*

The relative skill of those in the art is high, generally that of a PHD/MD with several years of practical experience and would have been aware of the Cecil reference discusses in (2) above. Thus, the ones of skill in the art at the time the claimed invention was made would have been aware of the impracticability of one drug for treating all forms of cancer and of the below discussed level of unpredictability in the art.

*4) Level of predictability in the art.*

The cancer treatment art involves a very high level of unpredictability as demonstrated by the state-of-the-art with regard to the treatment of specific cancers with specific agents and has long been underdeveloped with regard to the treatment of cancers broadly (see discussion in section *2)* above on the state of the prior art). The lack of significant guidance from the present specification or prior art with regard to the actual treatment of all types of cancer cells in a mammal, including a human subject, with the claimed active ingredients makes practicing the claimed invention unpredictable.

*5) Amount of direction or guidance provided by the inventor & 6) Presence or absence of working examples.*

The specification at pages 38-40 and Table 1 teaches the specific treatment of breast, ovarian, chronic myeloid leukemia (CML), acute myeloid leukemia (AML), multiple myeloma, colon, prostate, lung, and brain cancers, in corresponding cell lines and in *in vivo* mouse xenograft models with the claimed quinolinone compound.

*7) Breadth of claims.*

The claims are very broad and inclusive of cancer cells and tumors generally. The breadth of the claims exacerbates the complex nature of the subject matter to which the present claims are directed. The claims are extremely broad due to the vast number of possible cancer types represented by the term "cancer."

*8) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.*

The specification does not enable any person skilled in the art to which it pertains (i.e. chemotherapy and treatment of cancer) to make or use the invention commensurate in scope with the claims. The lack of adequate guidance from the specification or prior art with regard to the actual treatment of all cancers with the claimed quinolinone compound fails to rebut the presumption of unpredictability existent in this art. Applicants fail to provide the guidance and information required to ascertain which particular type of cancer the claimed anticancer agent will be effective against without resorting to undue experimentation. Applicant's limited disclosure with respect to

treatment of a variety of cancers (see Table 1, pages 38-40) with the claimed quinolinone compound is noted but does not demonstrate treating all cancers.

Absent a reasonable *a priori* expectation of success for using a specific chemotherapeutic agent/combination to treat any particular type of cancer, one skilled in the art would have to extensively test many various tumor types. Since each prospective embodiment, and indeed future embodiments as the art progresses, would have to be empirically tested, and those which initially failed tested further, an undue amount of experimentation would be required to practice the invention as its is claimed in its current scope, because the specification provides inadequate guidance to do otherwise.

***Pertinent Art:***

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

- Renhowe et al. (WO 02/22598 A1). Renhowe teaches administration of the instantly claimed compound and pharmaceutically acceptable forms thereof, for the treatment of cancer. The reference lists the instantly claimed compound (4-amino-5-fluoro-3-[5-(4-methyl-4-oxidopiperizin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one) at p. 155, line 21. Renhowe does not teach the specific limitations of Cmax, AUC, or specific dosages as instantly claimed.

***Summary***

Claims 1-38 and 49-58 are rejected. No claims are allowed.

Contact Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy A. Lewis whose telephone number is (571) 272-2765. The examiner can normally be reached on Monday-Friday, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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